

AD_____

Award Number: W81XWH-04-C-0083

TITLE: Internet-Based Cervical Cancer Screening Program

PRINCIPAL INVESTIGATOR: David C. Wilbur, M.D.
Barbara A. Crothers
John H. Eichhorn, M.D.
Min S. Ro, M.D.
Jeffrey A. Gelfand, M.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

REPORT DATE: May 2008

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-05-2008		2. REPORT TYPE Final		3. DATES COVERED (From - To) 15 MAR 2004 - 14 DEC 2007	
4. TITLE AND SUBTITLE Internet-Based Cervical Cancer Screening Program				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-04-C-0083	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) David C. Wilbur, M.D.;Barbara A. Crothers;John H. Eichhorn, M.D.;Min S. Ro, M.D. Jeffrey A. Gelfand, M.D. E-Mail: dwilbur@partners.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Massachusetts General Hospital Boston, MA 02114				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT This project explores the combination of computerized automated primary screening of cervical cytology specimens in remote sites with interpretation of device-selected images transmitted via the Internet. The project is in 3 phases: 1) hardware/software and interface development and end user training with a 200 case pilot study; 2) a 500 case prospective pilot study with hardware/software adjustment, with the development of clinically applicable specimen triage and management guidelines; and 3) a 5000 case prospective clinical trial of the completed system, with report and development of a training and operation manual. During this report period, phase 2 patient accrual was completed at the Massachusetts General and Walter Reed sites. Modifications to the image acquisition and reading/reporting software have been completed. All phase 2 patients have been entered into the system and are ready for reading (which will take place by July 2008). Preliminary planning for phase 3 is near complete with IRB submissions planned for summer 2008.					
15. SUBJECT TERMS Telecytology, cytopathology, telemedicine, cancer screening, health care information systems, cervical cancer					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	23	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	5
Body.....	6
Key Research Accomplishments.....	10
Reportable Outcomes.....	11
Conclusion.....	12
References.....	NA
Appendices.....	13

Introduction

Cervical cancer is theoretically completely preventable by effective screening using cervical cytology methods (the Pap test). The process of preparing and interpreting Pap tests remains one of the last high-volume manual processes in the clinical laboratory. Recent technological advances in specimen preparation and computerized primary screening make automated approaches to cervical cancer screening possible. In addition, advances in information technology have facilitated the Internet transmission and archival storage of digital images and other clinical information. The combination of automated preparation and screening of cervical cytology specimens, with Internet transmission of selected images, and remote interpretation and reporting of results has not been previously attempted.

This project develops a highly automated cervical cytology screening system, a software interface capable of transmitting and presenting images to remote reading stations, with facility for immediate results reporting back to the specimen source. Clinical studies utilizing this developed system will be performed to test accuracy and functionality against the current on-site manual screening process. Primary development of the system has been accomplished at the Massachusetts General Hospital (MGH) site and reading stations have been installed at MGH and at Walter Reed Army Medical Center (WRAMC). A phase 1 pilot study has been completed, data has been analyzed and reported (see 2008 publication in American Journal of Clinical Pathology - attached). Patient accrual for the phase 2 study targeting 500 prospectively obtained, consented patients has been completed (356 patients finally enrolled) following a very lengthy delay due to US Army IRB oversight approval processes (Office of Research Protections) as reported in the 2007 Annual Report. Reading/reporting/Analysis of this phase will be complete in July 2008. Preplanning for the final phase 3 clinical trial to be performed with the 121st Army Hospital in Seoul, Korea is near complete with an IRB submission planned for summer of 2008 and patient accrual to begin as soon as approval is granted.

Body

The following is a summation of the work completed to the present time based on the project's accepted Statement of Work. Details follow below in an expanded version of the Statement of Work:

Statement of Work

Task 1: Complete hardware, software and network development required for testing of the internet-based cervical cytology screening system

- a) Modify the FocalPoint device to accept, process and analyze ThinPrep specimens - **completed**
- b) Adapt FocalPoint hardware for internet transmission of digital images from ThinPrep and SurePath specimens - **completed**
- c) Adapt commercial software (Wellogic) to permit rapid and secure transmission of digital images to remote review stations - **completed**
- d) Procure and install remote microscopy stations (2) - **completed**
- e) Adapt commercial software/hardware (Wellogic) to allow secure, automated reporting of cervical cancer screening results - **completed**
- f) Adapt commercial software (Wellogic) to integrate screening results reporting with medical decision support system - **All Phase 2 modifications have been made and analyzed for proper functionality.**
- g) perform initial testing of integrated hardware/software/network - **completed**

Task 2: Develop morphology and terminology for digital images and perform pilot clinical trial

- a) Develop a set of learning cases with known diagnostic outcome - **pilot set of 200 cases completed (100 SurePath, 100 ThinPrep).**
- b) Develop morphologic criteria for accuracy of interpretation - **Phase 1 completed, pending Phase 2 modifications (July 2008).**

c) Develop reporting terminology appropriate for case management - **Phase 1 completed, pending Phase 2 modifications (July 2008).**

d) Develop medical decision support algorithms - **Phase 1 completed, pending Phase 2 modifications (July 2008).**

e) Perform pilot trial using a set of 500 unknown specimens to identify preliminary system performance characteristics - **This is a Phase 2 task. Patient accrual has been completed at MGH and Walter Reed sites.**

f) Modify procedures/equipment based on pilot trial results - **Phase 2 modifications completed.**

g) Develop training methods/materials for clinical practice - **Phase 2 modifications completed.**

Task 3: Complete large, prospective clinical trial of the performance of the internet-based system compared to conventional on-site screening.

a) Develop and receive approval for clinical trial protocol and consent forms -**Phase 3 protocols required modification based on information learned to date in phase 2. Final protocol is currently being prepared for submission to local IRBs and ORP. (planned submission summer 2008)**

b) Install equipment at selected sites - **Completed at MGH and Walter Reed sites. Installation at 121st Army Hospital will await IRB approval. Preplanning for this installation has been investigated and all necessary arrangements have been made to implement immediately upon receipt of necessary regulatory approvals.**

c) Train clinical personnel participating at selected sites - **phase 3 task**

d) Conduct the clinical trial - **phase 3 task**

e) Perform trial data analysis - **phase 3 task**

f) Prepare report of trial with implementation recommendation -**phase 3 task**

Expanded Discussion

A) Phase 1 of the project has been completed. This Phase included:

- 1) development of hardware, software, and interfaces between computerized scanning device and Internet-linked servers and reading stations.
- 2) development of a 200 case test set of slides with known reference diagnosis (100 SurePath and 100 ThinPrep slides)
- 3) analysis of the test set on the prototype system with interpretation by 6 individuals (3 cytotechnologists, 3 pathologists)
- 4) data analysis
- 5) reporting of the data in 3 abstracts presented at the US-Canadian Academy of Pathology Annual meeting (February 2006)
- 6) development of training materials to guide and improve performance
- 7) submission of revisions/improvements to software

Comments: Phase 1 showed a successful first feasibility trial of this system. 191 cases were included in the analysis (SP-101, TP-90; 99-NILM, 4-ASC-US, 3-ASC-H, 4-AGC, 63-LSIL, 18-HSIL). ≥ 3 reviewers agreed on the correct general categorization for unsatisfactory/normal in 87%, and for abnormal in 83%. For specific Bethesda interpretation, ≥ 3 reviewers agreed on the correct categorizations as follows: ASC-US - 75%, ASC-H - 100%, AGC - 25%, LSIL - 83%, HSIL - 94%. These results indicate that correct triage of abnormal cases could be performed at a sensitivity very comparable to the manual screening standard. In addition it was noted during the data analysis/training phase, that a substantial number of the "missed" cases had to do with experience of the observers in identifying clues present in the review station images or with institutional "biases," meaning differences in interpretations that could be traced to practice setting differences between MGH and WRAMC. A new publication detailing the results of the successful phase 1 trial has been published as the "lead" article in the American Journal of Clinical Pathology. (pdf of article attached) The reference is:

Eichhorn JH, Buckner L, Buckner SB, Beech DP, Harris KA, McClure DJ, Crothers BA, Wilbur DC.
Internet-based gynecologic telecytology with remote automated image selection: results of a first-phase developmental trial. Am J Clin Pathol. 2008 May;129(5):686-96.

B) Phase 2 of the project is nearly complete

After significant delays as detailed in the 2007 Annual report and reiterated below, the phase 2 patient accrual has been completed. With a target of 500 patients between MGH and Walter Reed sites, 356 were finally enrolled. It was felt by the site investigators that this accrual was sufficient to perform the trial adequately and it was necessary to close the enrollment due to the difficulty in consenting patients at the respective busy practice clinics. Wellogic reading/reporting system modifications required significant work as the company had migrated their information systems to a new operating system version platform since phase 1 work had been completed. The reading/reporting package required "migration" to this new platform via a series of software modifications and trials. This process was complicated by the "glitches" that developed (as might be expected in a software upgrade) which required the database to be purged and reloaded multiple times. Patients enrolled have now been entered into the registration

system, slides have been scanned and reconciliation of the images and patient demographic information has been completed. Reading of the specimens followed by data analysis will take place by July 2008.

Phase 2 timeline

- 1) Local IRB approvals were granted for Phase 2 at MGH and WRAMC
- 2) US Army "oversight" IRB (Office of Research Protections - ORP) required review submitted - 5/17/2005.
- 3) ORP requested revisions - 1/3/2006
- 4) Revisions submitted to ORP - 2/20/2006
- 5) ORP final approval for WRAMC was granted on 8/3/07.
- 6) ORP final approval for MGH was granted on 2/12/07.
- 7) Patient accrual completed on 11/30/07.
- 8) Software modifications to the Wellogic reading/reporting system completed on 4/15/08.
- 9) Patients and specimens accessioned to the system completed on 5/20/08.
- 10) Study staff retraining to take place (6/1-6/30/08)
- 11) Reading to commence 7/1/08.
- 12) Analysis to be completed by 7/30/08.

C) Phase 3 changes since the last Annual Report

- 1) The Phase 3 protocol is being prepared at the time of this report. Significant modifications are being planned to this protocol based on experienced gained in phase 2. Submission planned in summer of 2008.
- 2) An assurance was obtained for research to be performed at the 121st Army Hospital in Seoul, Korea via the Tripler Army Medical Center.
- 3) All initial arrangement have been made with vendors (Becton Dickinson/TriPath, Wellogic, Zeiss) to insure that installations in Korea can be accomplished rapidly following regulatory approvals for the phase 3 protocol.

Key Research Accomplishments

- 1) Assurance obtained for Phase 3 oversight at 121st Army Hospital via Tripler.
- 2) Patient accrual for phase 2 completed at MGH and Walter Reed sites.
- 3) Modifications have been completed for the reading/reporting station software (Wellogic) based on outcomes of Phase 1.
- 4) All issues based on operating system platform changes (Wellogic) have been resolved.
- 5) Preplanning for phase 3 protocol development is near complete (summer 2008)
- 6) A no cost annual extension has been approved for this project. (at the time of this writing we have received email notification of this extension but have not received the formal documentation)

Reportable Outcomes

1) Final publication of pilot study publication.

Eichhorn JH, Gelfand JA, Brauns TA, Crothers B, Wilbur DC. A Novel Automated Screening and Interpretation Process for Cervical Cytology Using Internet Transmission of Low Resolution Images: A Pilot Study. Cancer (Cancer Cytopathol) 2005;105:199-206

2) Publication of Phase 1 results complete.

[Eichhorn JH, Buckner L, Buckner SB, Beech DP, Harris KA, McClure DJ, Crothers BA, Wilbur DC. Internet-based gynecologic telecytology with remote automated image selection: results of a first-phase developmental trial. Am J Clin Pathol. 2008 May;129\):686-96.](#)

Conclusions

- 1) Phase 2 trial is nearing completion - patient accrual has been completed; all patients have been accessioned into the system and all slide have been scanned; retraining of study personnel is ongoing; all software modifications have been completed.
- 2) Assurance has been obtained for 121st Army Hospital in Seoul, Korea via Tripler.
- 3) Preplanning for phase 3 IRB protocol submission is near complete.
- 4) All arrangements are in place for immediate placement of instrumentation at the Korea site following regulatory approvals of the phase 3 protocol.

Appendices/Attachments

- 1) PDF file of the American Journal of Clinical Pathology 2008 lead article detailing the phase 1 results.

Internet-Based Gynecologic Telecytology With Remote Automated Image Selection

Results of a First-Phase Developmental Trial

John H. Eichhorn, MD,^{1,2} Leigh Buckner, CT(ASCP),³ Sally Beth Buckner, CT(ASCP),⁴ David P. Beech, CT(ASCP),¹ Kimberly A. Harris, MM,⁵ Douglas J. McClure, MIM,⁵ Barbara A. Crothers, DO,³ and David C. Wilbur, MD^{1,2}

Key Words: Cervical cytology; Automated screening; Internet; Web-based software; Telepathology; Telecytology

DOI: 10.1309/GRAV16QP8JR5XTPF

Abstract

A retrospective set of 191 gynecologic cytology slides with reference interpretations was run on an automated screening device that selects fields of view (FOVs) based on a hierarchical probability of abnormality being present. An interface was developed between the device and a remote server using customized image review software. FOVs were reviewed by 3 cytotechnologists and 3 cytopathologists, and binary triage (unsatisfactory for evaluation/negative for intraepithelial lesion or malignancy [NILM] vs “abnormal” [neither unsatisfactory nor NILM]) and specific interpretations were done. No morphologic training before FOV review was provided.

Three or more reviewers agreed on the correct categorization of NILM/unsatisfactory in 89% (85/96) and abnormal in 83% (79/95). Three or more reviewers triaged cases to abnormal as follows: atypical squamous cells of uncertain significance, 83% (5/6); atypical squamous cells, cannot exclude high-grade lesion, 100% (3/3); low-grade squamous intraepithelial lesion (SIL), 83% (52/63); high-grade SIL, 94% (17/18); and atypical glandular cells, 40% (2/5).

This procedure may have comparable sensitivity and specificity and possibly could provide effective initial triage to further evaluation. A review of individual cases suggests that further accuracy can be achieved with additional training and experience.

We previously hypothesized that the melding of 2 technologies, the Internet and computerized automated scanning, could lead to the provision of effective cervical cancer screening programs for countries lacking a trained cytology workforce and to an efficient, economical, and centralized way of triaging specimen data. In a pilot study, we showed that satisfactory and reliable interpretations of device-selected, electronically transmitted images can be made on a computer monitor, without manual microscopy.¹

The instrument used in that study, the FocalPoint screening system for cervical cytology (Becton Dickinson/TriPath Imaging, Burlington, NC), is used in many laboratories to triage cases to no further review or complete, manual review. Studies have shown that the use of this automated device allows cytologists to efficiently and reliably identify more abnormal cases than manual screening alone.²⁻⁴ This device also has 3 features that make possible the Web-based evaluation of device-selected images: (1) Up to 30 fields of view (FOVs) are selected using a proprietary algorithm based on a probability of that FOV containing cellular abnormality.⁴ (2) FOVs are arranged in a hierarchical rank order based on this probability. (3) The FOV images are black and white and low resolution, so that in JPEG compressed format, they are suitable for rapid digital transmission using Internet conduits of modest bandwidth. This image-capture capability had initially been engineered into the FocalPoint device to allow for the accurate localization of FOVs to observers during subsequent manual microscopic review, and, therefore, the images are linked to slide location ■ **Image 1**.

In our previous study,¹ the FOV images were transmitted as e-mail attachments, which made their display and manipulation cumbersome and inefficient. The image attachments for

each case had to be bundled and sent to the specific electronic address of the reviewer. In any clinical application, the resulting diagnoses would have had to be further delivered to other specified addresses for hierarchical review and/or consultation. The present study was designed to ameliorate those limitations by using a secure Web site and software that permits a variety of image display options.

The software application was custom designed for the efficient display and manipulation of FOV images, the retrieval of demographic and device-generated information, reporting capabilities, and data storage. Demographic data and device-captured images from individual cases were uploaded to a remote server, queued, and made available to assigned persons for review. A secure Web site displays the interpretations and images to additional individuals with access for further processing or reporting. Such a system allows for the following: (1) distribution of case images to people with diagnostic expertise, who may be in remote locations; (2) less transportation of perishable materials; (3) timely, encrypted transmittal of device-generated images and interpretations; (4) communication of results to patients, caregivers, or both, who may be in a remote location or in transit; and (5) efficient, economical triage of patients to additional clinical evaluation, testing, treatment, or any combination thereof.

The present study augments the scope of our prior study with a much larger population of cases, use of SurePath (Becton Dickinson/TriPath) and ThinPrep (Cytec, Marlborough, MA)

liquid-based samples, more diagnosticians, and more reading locations. Our goal was to test the reliability of Web-based image review for clinically meaningful interpretative groups. As in the pilot study, the goal was to distinguish, by means of primary triage, cases that require prompt intervention or further clinical evaluation from those that do not.

Materials and Methods

The study protocol was reviewed and approved by the institutional review boards at all investigational sites. The study population consisted of a set of liquid-based SurePath and ThinPrep cervical cytology slides from reference cases with known diagnoses from the files of 2 participating institutions. Interpretations were made using the criteria of the 2001 Bethesda System.⁵

An interface was established between a FocalPoint GS gynecologic screening device (Becton Dickinson/TriPath) located in Redmond, WA, and a computer server located in Cambridge, MA, using custom-designed, Web-based image and data acquisition and review software (Consult, Wellogix, Cambridge, MA) that automatically queries the FocalPoint database at regular intervals during the screening process. The software was developed in consultation with the investigators to address the specific needs of the project. The software application is based on an existing one that has been certified

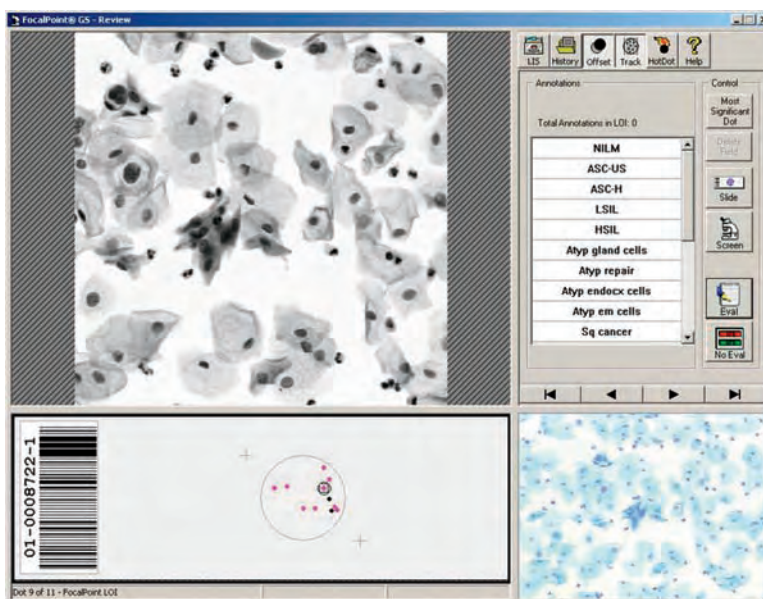


Image 1 FocalPoint gynecologic screening (GS) reviewing station showing a black and white image of the field of view (FOV) captured in the upper left part of the instrument (box) and corresponding microscopic image in the lower right. Note the FOV locations illustrated in the slide schematic at the bottom of the Image with the current FOV highlighted. Also note the square image captured by the device. The circular FOV forms the basis for the device's final analysis and is the area reviewed in the microscope in the commercial version of the FocalPoint GS system.

as compliant with the Health Insurance Portability and Accountability Act of 1996 for use in patient care settings.

Web site-based image review and data management software were developed for the present study to overcome the limitations inherent in the use of e-mail transmission and case review. The custom-designed software used in this study incorporated the following capabilities: (1) entry of clinical and demographic data of individual cases and linkage to captured images; (2) upload of specimen-derived images that are

device selected from an automated instrument at a remote site; (3) encryption of transmitted data and images; (4) secure storage of case-specific data and images; (5) orderly presentation of clinical data and images on a computer monitor; (6) access at the Web site to individual cases or to lists of cases, by registered cytotechnologists, cytopathologists, clinicians, and patients; (7) presentation of thumbnail FOV images in rank order **Image 2** and **Image 3**; (8) full-screen presentation of any 1 image, panels of 4 or 9 enlarged sequential images (with

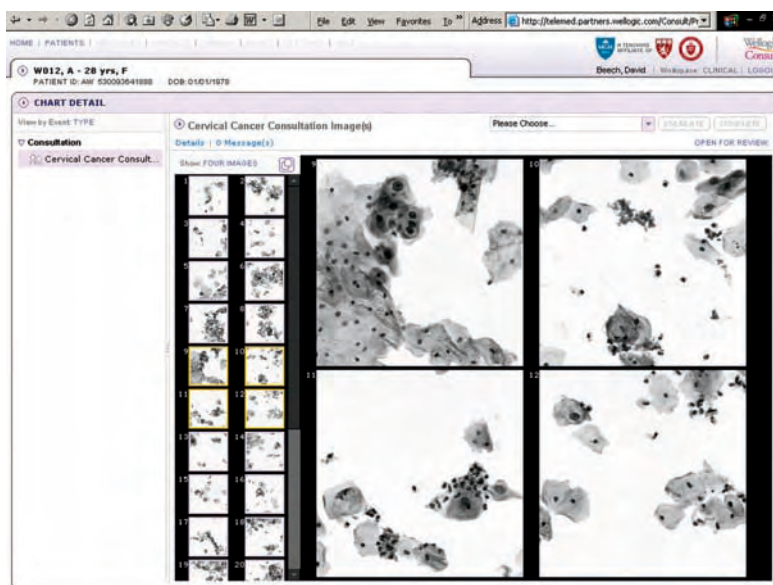


Image 2 Cases were accessed on a Web site with retrieval of images that had been uploaded to a remote server from the automated screening device; 30 JPEG images with the highest probability of abnormality are displayed in rank order (left), with an adjacent scroll tab. A panel of 4 selected highlighted images (fields of view 9-12) is enlarged (right). LSIL. ThinPrep slide.

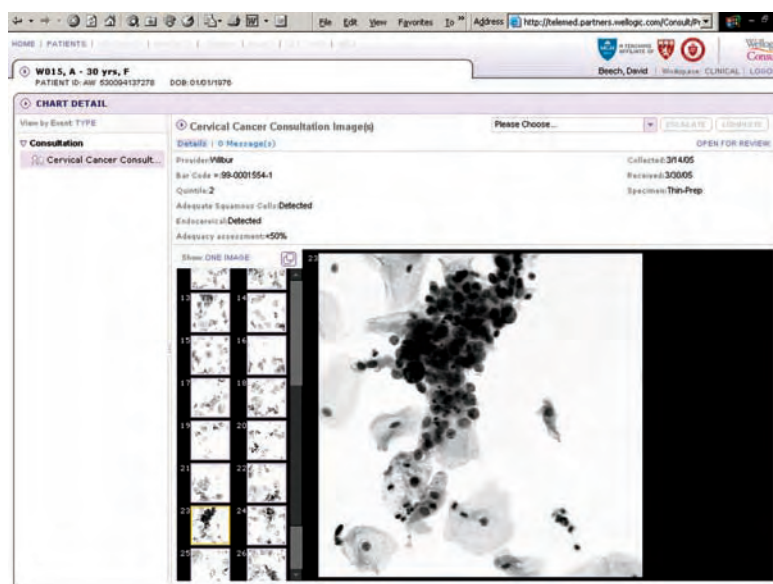


Image 3 Shown are 30 JPEG images in rank order according to probability of abnormality (left), enlarged view of JPEG image 15 (right), and drop-down view of specimen details (top), including distribution quintile and adequacy. High-grade squamous intraepithelial lesion involving glands. ThinPrep slide.

selection of the “starting” image) (Image 2), or of 4 enlarged nonsequential images (with point-and-click selection from thumbnail images); (9) presentation of clinical (age, reproductive, and menstrual status) and device-generated (distribution quintile, computer-assessment of adequacy) data from a drop-down folder tab on the monitor (Image 3); (10) recording of each interpretation on every case by a cytotechnologist, cytopathologist, and (if needed) consultant; (11) electronic communication between any or all people responsible for any individual case; and (12) presentation of the finalized evaluations of selected cases to clinicians, patients, or both.

Demographic information for each slide was entered manually into the slide review database. The slides were tagged with bar codes, stripped of other identifiers, and scanned at the remote site on the FocalPoint GS system. A set of up to 30 of the highest scoring FOV images were captured in a JPEG compressed format (image size, 12-16 KB each). The FocalPoint GS system captures only black-and-white images, each of which corresponds closely to an approximately $\times 200$ microscopic magnification when viewed on a monitor. Of note, the image captured by the device represents only the central area of a $\times 200$ magnification FOV that, in the commercial application of the FocalPoint GS device, is intended to be viewed as a full circular microscopic FOV. Hence, each image used in the study does not contain the entire FOV intended to be viewed in the normal operation of the device. Sets of JPEG images for each case were transmitted over the Internet and uploaded to the remote server. For each case, 30 JPEG images were device generated and transmitted unless fewer FOVs were selected by the scanner, as occurred in 22 cases of low cellularity (for which 5-29 FOVs [mean, 22 FOVs] were selected). To capture maximal information from the abbreviated FOVs, 30 images were selected for review; in the intended use of the device, only the top 10 scoring FOVs are used. The maximum file size per case was less than 500 KB. Known demographic information (eg, age and menstrual status) and standard FocalPoint device-generated data (distribution quintile, computer assessment of adequacy) were entered into the database for each case.

The review stations were the standard personal computers (Microsoft Windows 2000 Professional operating system, Microsoft Explorer browser, Microsoft, Redmond, WA) used by the reviewers in their secure institutional networks, augmented by high-resolution 19-inch LCD monitors to enhance the clarity of images. The monitor settings and image display options were standardized across institutions. The study did not seem to be affected by network delays at either institution. The software application displayed up to 30 thumbnail images for each case in a panel on the left side of the monitor (Images 2 and 3). Each individual image could be displayed as a single large image or as a panel of 4 or 9 consecutive images at less than maximal enlargement, depending on the preference of

the observer. In addition, for image comparison purposes, any 4 selected nonconsecutive FOVs could be displayed together as a panel of enlarged images. Demographic and FocalPoint data for each case were accessed by using a drop-down tab. Interpretations for each case could be entered in a results field after image review and forwarded to another individual for final review (“escalate” tab), or submitted as a final diagnosis (“complete” tab).

Glass slides were not manually reviewed by any participant during the study, and the reviewers received no training in the evaluation of the black-and-white FOV images. Each of the study cases was interpreted independently by 3 ASCP-registered cytotechnologists (D.P.B., L.B., and S.B.B.) and 3 board-certified cytopathologists (B.A.C., J.H.E., and D.C.W.) who were masked to the reference diagnoses. During the study, an off-line worksheet was used that allowed the recording of participant observations in a format intended as an aid to future data analysis and further technique refinement. Reviewers annotated the reasons that a given interpretation was favored and features of each case that made evaluation difficult. For every case, they also recorded the first FOV for which an abnormality was suspected, the first FOV at which the final interpretation became fixed, and the specific FOVs that contained abnormalities or in which other observations were made. Assessments regarding adequacy and any other comments about each case were recorded.

Cases were interpreted as specifically as possible by the reviewers and then assigned to 1 of 2 categories: (1) negative for intraepithelial lesion or malignancy (NILM; normal findings, reactive changes, organisms) or unsatisfactory for evaluation; or (2) any cellular abnormality diagnostic of an intraepithelial lesion (or worse) or worrisome for its presence (high-grade squamous intraepithelial lesion [HSIL]; low-grade SIL [LSIL]; atypical squamous cells, cannot exclude high-grade lesion [ASC-H]; atypical squamous cells of uncertain significance [ASC-US]; or atypical glandular cells [AGC]). It was intended that this binary categorization would determine if the combination of automated screening and Web-based transmittal and presentation of images could be used to triage patients appropriately, with the cutoff point representing clinically significant lesions requiring further evaluation.

After reviewers had recorded their initial binary assessments for each case, their “trial” interpretations were compared with the reference diagnoses. All 6 reviewers met at 1 location to review the images of selected cases for which there were 1 or more discrepant interpretations, with simultaneous access to the images of these cases (from the Web site) and written observations that they had made at the time of masked review recorded in a computerized database. The potential sources of error were discussed at this time. The slides of cases for which all, or nearly all, reviewers incorrectly categorized the binary triage compared with the reference diagnosis were screened

manually by the investigators to confirm or change a reference diagnosis for data analysis purposes.

A comparison was done of reviewer categorization (binary triage) vs the reference diagnosis for each case and tabulated based on how many reviewers achieved the correct result. The numbers of reviewers correctly triaging the cases into these 2 categories were also tabulated for each Bethesda diagnostic group for the reference cases. In addition, rates of sensitivity [True Positive/(True Positive + False Negative)] and specificity [True Negative/(True Negative + False Positive)] were calculated at the level of agreement by 3 or more reviewers because it was postulated that this degree of concordance indicated that a correct interpretation *could* have been made in each case.

Results

The study set included 101 SurePath and 90 ThinPrep slides. We excluded 11 other ThinPrep slides from the study because they could not be adequately scanned by the FocalPoint device. In these cases, it seemed that scanning was impeded by technical problems such as coverslip placement, artifacts of preparation, and staining irregularities. Reference diagnoses included the following: HSIL, 18; LSIL, 63; ASC-H, 3; ASC-US, 6; AGC, 5; NILM, 93; and unsatisfactory for evaluation, 3 **Table 1**.

Images 2 and 3 and **Image 4** include representative device-captured FOV images from ThinPrep slides, and **Im-**

Table 1
Reference Diagnoses and Preparatory Method for 191 Study Cases

Bethesda Category ⁵	SurePath (n = 101)*	ThinPrep (n = 90)*
HSIL	6	12
LSIL	45	18
ASC-H	0	3
ASC-US	2	4
AGC	0	5 [†]
NILM	48	45
Unsatisfactory for evaluation	0	3

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.
* One slide per case.
[†] The slides from these cases were rescreened after the trial; 3 of 5 were diagnosed as NILM by majorities of reviewers, and these patients had subsequent surgical procedures that were negative.

age 5, **Image 6**, and **Image 7** show images from SurePath slides. The images derived from ThinPrep slides tended to have fewer cells for evaluation in each FOV than those produced from SurePath slides, and the cells in the images from ThinPrep slides were less evenly spread across the FOV. These findings directly relate to the lower cell concentration and increased “open” areas routinely present on each ThinPrep slide compared with the higher and more evenly distributed cellularity of a routine SurePath slide. SurePath slides, on the other hand, showed fewer well-focused cells and poorer overall image resolution, especially in hypercellular

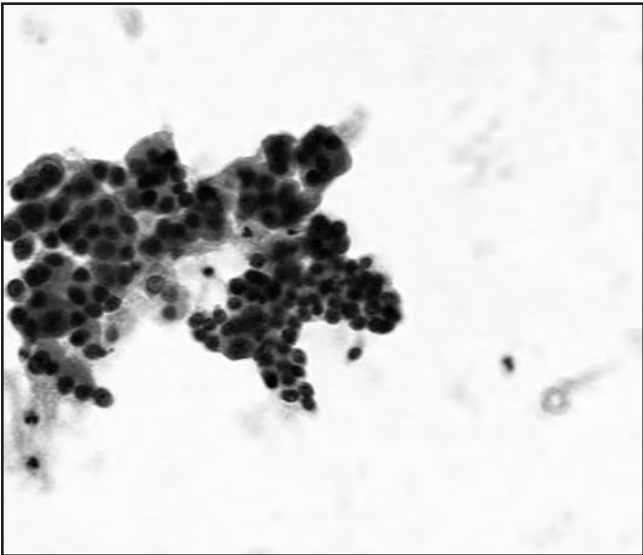


Image 4 Glandular cell atypia was difficult to assess on low-resolution JPEG images. Adenocarcinoma in situ. ThinPrep slide.



Image 5 Case judged negative for intraepithelial lesion or malignancy with abundant normal endocervical cells. The 3 reviewers not accustomed to screening SurePath slides called this case atypical.

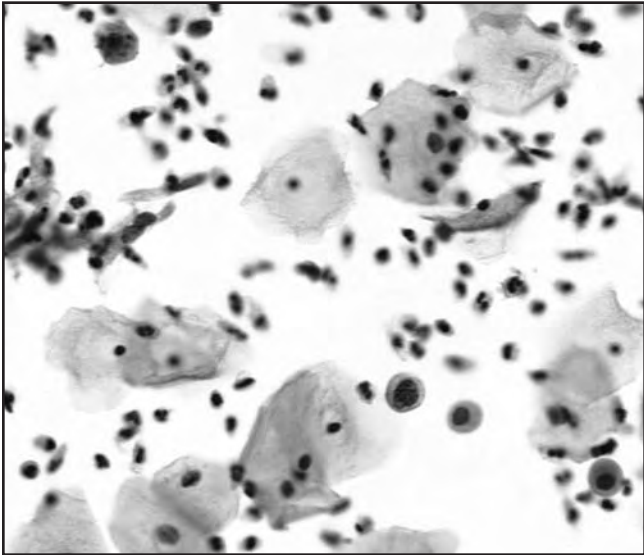


Image 6 High-grade squamous intraepithelial lesion cell (center right) and benign cells for comparison. Hypercellular fields of view sometimes had poorer resolution of the nuclei of atypical cells. SurePath slide.

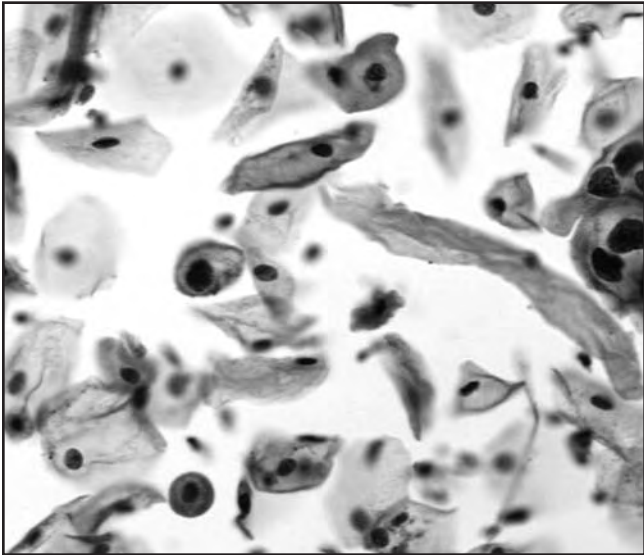


Image 7 Abnormal cells and cell clusters are not always positioned in the center of the selected field of view (FOV) owing to the full-field interpretation algorithmic method used in the FocalPoint system. Abnormal cells can be localized to any portion of the selected FOV. Low-grade squamous intraepithelial lesion. SurePath slide.

samples. This finding could be related to the characteristic 3-dimensional depth of routine SurePath slides, which might have led to more variability in the device-determined plane of focus.

The reviewers' ability to correctly assign the cases to either of the 2 categories, NILM/unsatisfactory or abnormal, is shown in **Table 2**. Three or more investigators agreed on the correct general categorization of NILM/unsatisfactory in 89% of cases (85/96) and abnormal in 83% of cases (79/95). This corresponds to a sensitivity of 88% and a specificity of 93% for binary categorization at the level of agreement by at least 3 reviewers. The ability of the reviewers to triage individual cases to the abnormal group and target a specific Bethesda category of reference diagnosis is shown in **Table 3**. For specific Bethesda interpretations, the frequencies at which 3 or more reviewers triaged the cases to abnormal were as follows: ASC-US, 83% (5/6); ASC-H, 100% (3/3); LSIL,

83% (52/63); HSIL, 94% (17/18); and AGC, 40% (2/5). That is, the reviewers' ability to triage to the abnormal group the cases with possible high-grade squamous lesions (HSIL or ASC-H) was better than their ability to assign low-grade squamous lesions (LSIL) to that category. A majority of the reviewers incorrectly categorized 7 (16%) of 45 SurePath LSILs and 4 (22%) of 18 ThinPrep LSILs, whereas a majority incorrectly assigned only 1 (6%) of 18 HSILs. These observations are consistent with the known sensitivity data of the FocalPoint screening device.^{4,6}

The data in Table 3 suggest that the system did not perform as well for glandular as for squamous cell abnormalities, but this apparent disparity was all but eliminated when the individual cases were examined more closely. When the slides (all ThinPrep) of the 5 cases of AGC were reexamined by the reviewers as a group, 3 cases were judged to have an incorrect reference diagnosis by majorities of the participants

Table 2
Comparison of Test and Reference Triage Groups*

General Category of Reference Cases	No. of Reviewers With Correct General Categorization							Total
	6	5	4	3	2	1	0	
NILM/unsatisfactory for evaluation	35	29	9	12	6	4	1	96
Abnormal	32	30	9	8	4	8	4	95

NILM, negative for intraepithelial lesion or malignancy.
* Data are given as number of cases.

Table 3
Reviewer Triage to Abnormal vs Bethesda Category (All Cases)*

Bethesda Category of Reference Cases	No. of Reviewers Triaging Cases to "Abnormal" Group							Total
	6	5	4	3	2	1	0	
ASC-US	0	1	2	2	1	0	0	6
ASC-H	0	0	2	1	0	0	0	3
LSIL	27	18	3	4	3	5	3 [†]	63
HSIL	1	9	6	1	0	0	1 [†]	18
AGC	0	1	0	1	1 [‡]	2 [‡]	0	5

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; FOV, field of view; HSIL, high-grade intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

* Data are given as number of cases.

[†] Reexamination of FOVs from these cases revealed no convincing abnormality, indicating device failure of abnormality localization to selected FOVs.

[‡] The slides from these 3 cases were rescreened after the trial and were interpreted as negative for intraepithelial lesion or malignancy by majorities of the participants; subsequent surgery failed to detect a glandular abnormality.

and to have shown no more than reactive glandular changes. In each of these 3 cases, no glandular lesion was identified after subsequent surgery (cone biopsy and endocervical and endometrial curettage, 2 cases; hysterectomy, 1 case). On the initial FOV review, 2 of these cases had been assigned to the NILM/unsatisfactory group by 5 reviewers and the other case by 3 reviewers.

Of the remaining 2 AGC cases, 1 patient had endometrial adenocarcinoma found by subsequent hysterectomy. When the device-selected FOVs of this case were reexamined, however, no convincing atypical glandular cells were found. This case had been called NILM by 4 participants and ASC-US by 2. Finally, 1 patient with a reference diagnosis of AGC had endocervical adenocarcinoma in situ in a subsequent hysterectomy specimen. This case (Image 4) had been called abnormal by 5 of 6 participants after FOV review, but there was little agreement on specific categorization: 2 called it cancer and 1 each called it LSIL, ASC-US, or AGC. Thus, of only 2 true AGC cases in the study, one lacked abnormal cells in device-selected FOV images and was missed on this basis, and the other had abnormal cells in the FOVs and correct binary triage by 5 of 6 reviewers. Differences in the specific categories to which this latter case was assigned may be related to difficulties in resolving fine details in small glandular cells.

In 4 cases with a squamous abnormality (SurePath LSIL, 2; ThinPrep HSIL, 1; ThinPrep LSIL, 1), none of the 6 reviewers gave an interpretation of abnormal. Reexamination of the 30 device-selected FOV images of each of the 4 cases revealed no convincing squamous abnormalities. The cases screened from SurePath slides (both containing LSIL) showed rare (1 or 2) dense blotches on the FOVs; these may be koilocytotic nuclei, but there was insufficient detail to be sure. In the cases from ThinPrep slides, subsequent biopsies confirmed the presence of squamous dysplasia that was severe in one case and mild in the other. The ThinPrep HSIL case appeared to contain many small cells of parabasal or metaplastic type, and it is possible that similarly sized dysplastic cells

may have been missed at the level of resolution of the FOV images. These 4 cases indicate that the abnormal cells in squamous lesions (particularly LSIL) may not be captured in the rectangular images captured by the automated device from the selected FOV.

The success of binary triage by the reviewers is separately shown by preparatory technique in **Table 4** and **Table 5** for the abnormal cases. There were differences in the composition of abnormal cases in these 2 study populations, how and where the reference sets were compiled, and the availability of follow-up data from subsequent procedures. Of 53 abnormal SurePath slides, 45 (85%) showed LSIL and none showed AGC; follow-up data were not readily available for some of these cases. There were fewer cases with ThinPrep slides (11 cases were initially eliminated from the study because their slides could not be adequately scanned by the FocalPoint device), but among the 42 abnormal cases in this set of slides, there was a broader distribution of Bethesda groups, including 18 LSIL (43%), 12 HSIL (29%), 5 AGC (12%), 4 ASC-US (10%), and 3 ASC-H (7%) cases. In this population, follow-up data from subsequent surgical procedures were available for all cases with abnormal cytology. Moreover, the reviewers differed in their experience with each of the 2 liquid-based methods: reviewers at one institution had experience with both types of slides but had been routinely using SurePath slides in clinical practice, whereas reviewers at the other institution had little or no recent experience with SurePath slides, having used the ThinPrep method exclusively in their practice.

As in our previous study,¹ FOV images displayed on a computer monitor showed poorer resolution for a given degree of magnification than would have been achieved by standard light microscopy. Their plane of focus is set by the automated instrument and cannot be manipulated. These features and the lack of a full-color spectrum made the evaluation of fine or subtle nuclear and cytoplasmic detail more challenging than in light microscopy, particularly for the smaller cells within a

Table 4
Reviewer Triage to Abnormal vs Bethesda Category (SurePath Cases)*

Bethesda Category of Reference Cases	No. of Reviewers Triaging Cases to "Abnormal" Group							Total
	6	5	4	3	2	1	0	
ASC-US	0	1	1	0	0	0	0	2
ASC-H	0	0	0	0	0	0	0	0
LSIL	21	12	2	3	3	2	2 [†]	45
HSIL	0	3	3	0	0	0	0	6
AGC	0	0	0	0	0	0	0	0

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; FOV, field of view; HSIL, high-grade intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

* Data are given as number of cases.

[†] Reexamination of FOVs from these cases revealed no convincing abnormality, indicating device failure of abnormality localization to selected FOVs.

Table 5
Reviewer Triage to Abnormal vs Bethesda Category (ThinPrep Cases)*

Bethesda Category of Reference Cases	No. of Reviewers Triaging Cases to "Abnormal" Group							Total
	6	5	4	3	2	1	0	
ASC-US	0	0	1	2	1	0	0	4
ASC-H	0	0	2	1	0	0	0	3
LSIL	6	6	1	1	0	3	1 [†]	18
HSIL	1	6	3	1	0	0	1 [†]	12
AGC	0	1	0	1	1 [†]	2 [†]	0	5

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; FOV, field of view; HSIL, high-grade intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

* Data are given as number of cases.

[†] Reexamination of FOVs from these cases revealed no convincing abnormality, indicating device failure of abnormality localization to selected FOVs.

* The slides from these 3 cases were rescreened after the trial and were interpreted as negative for intraepithelial lesion or malignancy by majorities of the participants; subsequent surgery failed to detect a glandular abnormality.

given image. Each cytologist reported spending approximately 1 to 2 minutes per case on average to review the images and make an interpretation, although no attempt was made to do a formal time analysis in this first-phase study.

Discussion

In the United States, the incidence and mortality rates of cervical cancer have decreased 50% and 70%, respectively, in the 50 years since widespread screening programs were instituted.^{7,8} Other countries have also benefited greatly from population-based screening programs.⁹ Worldwide, however, cervical cancer continues to be a leading cause of death for young women who reside in countries without systematized screening programs.¹⁰ These regions lack an adequate pool of trained specialists to screen and interpret specimens. They typically lack funding for evolving new technologies such as liquid-based preparations, automated screening devices, and human papillomavirus testing. Even in the United States, laboratories experience fluctuating workloads out of synchrony with their available workforce, resulting in specimen backlogs.

Remote interpretation of automated device-selected

digitized images transmitted over the Internet has the potential to provide effective screening and clinical triage to individuals in these populations. "Proof of concept" was provided by a recent feasibility study in which it was shown that low-resolution images selected by an automated screening device and transmitted over the Internet as e-mail attachments could be adequately interpreted at a distant site without manual microscopy, using primary triage methods for clinically meaningful diagnostic categories.¹ An algorithm of remote review of a laboratory's total cervical cytology workload with triage of the most potentially abnormal cases to on-site review by the originating laboratory has the potential to select the "needles out of the haystack" for expedited review. In addition, laboratories could more effectively share personnel resources across distances without resorting to the shipment of glass slides, thereby easily redistributing the workload among available resources.

The use of customized Web site-based data management software facilitated the accommodation of more reviewers and reviewing stations in the present study than there had been in the previous one, thereby permitting the evaluation of a much larger population of cases. Multiple investigators could evaluate each of the cases at their own particular location, in any order, at their own pace, and with as many "visits" to the

cases as needed.

Although the FocalPoint system is approved by the US Food and Drug Administration (FDA) for automated scanning of SurePath slides, it can also be reconfigured for the assessment of ThinPrep slides, for which it has shown screening efficacy.¹¹ It is FDA approved for the screening of conventional smears as well, but the present study was designed to evaluate slides made from liquid-based preparations. We included both liquid-based slide types in the present study, not to compare the desirability of one method over the other, but to show that both can be used in such a system and to judge the special features of each type of preparation when evaluated on the monitor-based FOV reviewing platform. This was necessary because we anticipated that one or the other type of liquid-based preparation may be favored or in use in the target population of our subsequent studies or their intended applications. Differences in the images derived from the 2 types of samples were seen. ThinPrep slide images tended to have fewer cells per FOV than those from SurePath slides, and the cells were distributed less uniformly across each FOV. The images produced from SurePath slides, however, had poorer image resolution, especially in cellular samples, generally because a thicker layering of cells in these preparations produced more variability in the device-determined plane of focus.

Even though image quality and size were augmented by the use of larger, flat-screen monitors with better resolution than the monitors used in our prior study, the resolution of the FOV images still was not as optimal as that of standard light microscopy, and the fixed plane did not allow manipulation of cells that were not optimally focused when captured. In the present study, these limitations may have hindered the appreciation of fine cellular details in glandular cells, which tended to be small and to present in closely packed groups (Image 4), which led to difficulty in classifying a case of adenocarcinoma in situ (although it was recognized as abnormal by 5 of 6 reviewers). Conversely, 3 investigators working at hospitals that screen only ThinPrep slides tended to overcall glandular atypia from images derived from SurePath slides that had abundant normal endocervical cells (Image 5).

Despite a poorer focus and resolution of images derived from some SurePath slides that were hypercellular (because of a thicker layer of cells per FOV), HSIL was correctly recognized despite the small size from cellular features unaffected by these limitations, such as nuclear/cytoplasmic ratio, nuclear shape, and degree of hyperchromasia, compared with neighboring cells in the FOV image (Image 6). The reviewers noted that LSIL cells were easier to recognize than HSIL cells because of their larger nuclear dimensions and the occasional presence of human papillomavirus-associated cytopathic perinuclear halos.

The most abnormal cells, however, were not always

positioned near the center of the FOV (Image 7), nor were they always present in the FOVs that had been assigned the highest probability scores for having cellular abnormality. These observations relate to FocalPoint system programming because the device selects FOVs with the highest probabilities of cellular abnormality based on its assessment of the field "as a whole" and not of individual cells within the field or their position within it. Moreover, the computer algorithm used to assign these probabilities has an intended bias, based on training and prioritization, toward the detection of high-grade squamous lesions over the identification of other types of abnormality.

In follow-up group discussions, it seemed that some reviewers had been more bothered than others by the lack of a full-color spectrum, particularly in the evaluation of subtle differences in cytoplasmic characteristics of squamous metaplastic and high-grade squamous dysplastic cells, and that some investigators were more adept than others in making cellular and nuclear size comparisons from FOV images. Different reviewers developed their own preferred strategies of approach to individual cases using the display software, which probably evolved between review of early and later cases.

The reviewers' success in binary triage of the cases was analyzed at the level of agreement of 3 or more individuals (half the total number of viewers). This level of agreement was selected for this first-phase trial because most of the reviewers had no experience in the evaluation of black-and-white FOV images, none had used the Web-based image display software, no prior training in FOV assessment had been given, and some of the reviewers were familiar with one liquid-based preparation but not sufficiently with the other. It was hypothesized that if 3 or more of 6 observers were able to classify a case correctly, there was most likely good reason, and, hence, training would improve performance of the remaining 3 or fewer observers. At this level of agreement, sensitivity of 88% and specificity of 93% were obtained for the categorization of the cases into 1 of the 2 groups. When various threshold levels of abnormality were separately examined for cases with squamous abnormalities, the sensitivity of detection of HSIL or worse (94%) was better than the sensitivities at lower threshold levels (85% for LSIL or worse and 86% for ASC-US or worse) ■ **Table 6**. These figures compare favorably with reports of the sensitivity of manual screening reported in clinical trial settings. In the original FDA clinical trials for the FocalPoint screening system, overall sensitivity for binary triage of all abnormal cases (ASC-US or worse) was 78%, for LSIL or worse was 83%, and for HSIL or worse was 93%,⁴ figures that are very close to the results obtained in this study.

One limitation of the present study is the fact that

Table 6
Sensitivity of Detection of Various Squamous Abnormality Thresholds by at Least Three of Six Reviewers

Abnormality Threshold	Sensitivity (%)
ASC-US or worse	86
LSIL or worse	85
HSIL or worse	94

ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

abnormal cases were overrepresented in the current study population compared with the aforementioned prospective study.⁴ This difference could enhance the apparent sensitivity of detection owing to increased disease prevalence and, hence, heightened vigilance of observers. A prospective study to more thoroughly test these operating characteristics is underway at the time of this writing. When specific types of cellular abnormality were examined, it seemed that reviewers were better at recognizing as abnormal the cases that contained potential high-grade squamous lesions than cases with low-grade squamous abnormalities. Identification of glandular lesions remains a challenge to the system, as in the standard manual review process; however, these lesions generally represent a small minority of cases in actual practice.

We anticipate that the interpretation of FOVs can be improved with training and the development of strategies to compensate for the difficulties of FOV assessment in particular types of cases. The identification of common and recurring pitfalls in evaluation and of problematic types of cases will inform us in the assembling of study sets for the purpose of training. Can the quintile data provided by the instrument be used as an ancillary clue in individual cases? In separate studies, we are investigating the optimal number of FOVs for effective specimen triage and whether determinations of specimen adequacy can be made reliably. It also needs to be established if, and how often, diagnostic cells are present in the device-selected FOV (which is circular) but not in the captured JPEG image (which is rectangular and a centrally located subset of the larger circular field). For example, in the 4 squamous lesions (3 LSIL and 1 HSIL) that were missed by all reviewers, the abnormal cells were present on the slides but not in the rectangular JPEG images. Were they present at the periphery of the device-selected FOVs but outside the boundaries of the JPEG image? In the future, additional avenues of investigation might include the addition of color image capture, wider FOVs, and the making of virtual slide images for whole-slide manipulation and/or focusing. Possibly, virtual microscopy or whole-slide imaging might be used to identify solutions for

the shortcomings of static digital image transmission.

We are encouraged that Web-based interpretation of automated device-selected images transmitted electronically can permit optimization of interpretative expertise and potentially provide cytology screening services to populations that currently have none, enhance resource sharing between laboratories, and centralize cytology interpretation services. Reviewers will be further trained from study sets acquired from the present exercise in an attempt to further enhance the capability of interpreting FOV images in this system. In addition, a larger prospective trial with specimens from current patients is underway.

From the ¹Cytopathology Division, Massachusetts General Hospital; ²Department of Pathology, Harvard Medical School; and ³Center for Connected Health, Partners Health Care, Boston; and the Departments of Pathology, ³Cytopathology Service, Walter Reed Army Medical Center, Washington, DC; and ⁴National Naval Medical Center, Bethesda, MD.

Preliminary work was supported by the Edmund C. Lynch, Jr, Cancer Fund. Ongoing portions are supported by the US Army Medical Research and Materiel Command, contract W81XWH-04-C-0083.

The Walter Reed Army Medical Center Human Use Committee and the Massachusetts General Hospital Human Research Committees approved the research. This portion of the study was a pilot project using existing patient specimens and was granted an exemption from the institutional review boards.

Presented at the Annual Meeting of the United States and Canadian Academy of Pathology; February 11-17, 2006; Atlanta, GA.

Address reprint requests to Dr Eichhorn: Warren 105C, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114.

Acknowledgment: James E. Stahl, MD, CM, MPH, provided consultative advice on statistical evaluation.

Disclosure: The opinions or assertions contained herein are the private views of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or US Government. Dr Wilbur is a member of the speakers' bureau and has served as a principal investigator on institutional grant support from TriPath Imaging and has served as a principal investigator on institutional grant support from Cytoc.

References

1. Eichhorn JH, Brauns TA, Gelfand JA, et al. A novel automated screening and interpretation process for cervical cytology using the Internet transmission of low-resolution images: a feasibility study. *Cancer*. 2005;105:199-206.
2. Richart RM, Nelson AC, Wood T. Clinical test results for automated quality control and primary screening of cervical smears using the NeoPath AutoPap 300 System [abstract]. *Acta Cytol*. 1994;38:805.
3. Stevens MW, Milne AJ, James KA, et al. Effectiveness of automated cervical cytology rescreening using the AutoPap 300 QC System. *Diagn Cytopathol*. 1997;16:505-512.

4. Wilbur DC, Prey MU, Miller WM, et al. The AutoPap system for primary screening in cervical cytology: comparing the results of a prospective, intended-use study with routine manual practice. *Acta Cytol.* 1998;42:214-220.
5. Solomon D, Nayar R. *The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria and Explanatory Notes*. 2nd ed. New York, NY: Springer-Verlag; 2004.
6. Wilbur DC, Parker EM, Foti JA. Location-guided screening of liquid-based cervical cytology specimens: a potential improvement in accuracy and productivity is demonstrated in a preclinical feasibility trial. *Am J Clin Pathol.* 2002;118:399-407.
7. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med.* 2000;132:810-819.
8. Boring CC, Squires TS, Tong T, et al. Cancer statistics, 1994. *CA Cancer J Clin.* 1994;44:7-26.
9. Sankaranarayanan R, Budukh AM, Rajkumar R. Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ.* 2001;79:954-962.
10. Ferlay J, Parkin DM, Pisani P. *Globocan 1: Cancer Incidence and Mortality Worldwide*. Lyon, France: IARC Press; 1998. IARC CancerBase 3.
11. Lee JLJ, Kuan L, Ellison D, et al. Evaluation of the NeoPath AutoPap 300 QC System on Cytoc ThinPrep-Prepared slides [abstract]. *Acta Cytol.* 1996;40:1043-1044.